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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,523	11/21/2003	Kenneth J. Rothschild	AMBER-08501	3365

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EXAMINER	
JOIKE, MICHELE K	

ART UNIT	PAPER NUMBER
1636	

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03/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,523	ROTHSCHILD ET AL.	
	Examiner	Art Unit	
	MICHELE K. JOIKE	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 20, 2007 has been entered.

Claims 1, 9 and 11-13 are pending and examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "said primer" in line 4. There is insufficient antecedent basis for this limitation in the claim. Applicants claim an oligonucleotide pre-primer in line 2. As Applicants have pointed out in their response there is a difference between a pre-primer and a primer.

This is a new rejection necessitated by amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9 and 11-12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Little et al (US Patent No. 6,207,370) in view of Garvin et al (US Patent No. 6,329,180; IDS Ref. 1).

Little et al teach a reaction mixture for amplifying a nucleic acid as a means of detecting and isolated a mutation in a genetic region, the reaction mixture comprising

a) a first oligonucleotide primer comprising i) a T7 promoter sequence, ii) a ribosome binding site sequence, iii) a start codon, iv) a sequence coding for a first epitope marker and v) a first region of complementarity to a region of the APC gene; and

b) a second oligonucleotide primer comprising i) at least one stop codon, and ii) a sequence encoding for a second epitope marker,

wherein said first epitope marker is SEQ ID NO: 5, a hexahistadine tag (see entire document, especially column 3, lines 10-21 and 50-58; column 4, lines 20-22; column 9, lines 38-49; column 14, lines 1-3, 31-38, 51-55; column 15, lines 19-29). Little et al also teach the use of other tags for use in their method including a 10-residue sequence from c-myc, the pFLAG system, and a 16 amino acid portion of the *Haemophilus influenza* hemagglutinin protein (see column 14, lines 45-58). The

primers taught by Little et al can be used to amplify target genes which are not limited to APC, but include, e.g., BRCA1, BRCA2, dystrophin gene, CFTR, etc. (see column 4, lines 10-25). Little et al also teach that in one embodiment, an RNA molecule encoding a target polypeptide can be translated in a cell-free extract, such as a reticulocyte lysate, a wheat germ extract, or a combination thereof (see column 3, lines 28-32). Finally, Little et al teach that the primer used in the reaction "typically contains 15-25 nucleotides" but may be longer or shorter depending on many factors, including temperature and source of primer and use of the method (see column 13, lines 35-44). Little et al also teach the use of mass spectrometry to determine the mass/identification of the translated protein (see, e.g., column3, lines 50-59 and column 26, lines 30-39).

Little et al do not explicitly teach this method wherein the first and second epitope markers are different and wherein the second epitope marker is selected from the group consisting of SEQ ID NOS: 6-9.

Garvin et al teach a kit and methods for detecting protein altering mutations in genes such as BRCA1 and BRCA2 (see entire document, including the Abstract and column 1, lines 21-36). The method comprises the use of a 5' primer that contains a T7 polymerase binding site, a sequence that allows translation initiation of mRNA, an in frame sequence coding for a FLAG epitope marker (Applicant's SEQ ID NO:7), and a 5' hybridization sequence "of sufficient length to allow the oligomer to hybridize to the non coding strand of the test sequence present in the genomic DNA or cDNA sample and to act as a primer for PCR. Usually 20 bases are enough" (see column 3, lines 59-67 and column 4, lines 1-26 as well as Garvin et al's SEQ ID NO:2). Garvin et al also teach

such method comprising the use of a 3' primer which comprises an inverse complement of sequence encoding a peptide tag and a sequence that hybridizes to a sequence at or adjacent to the 3' end of the coding strand of the test sequence. Most importantly, Garvin et al teach that in one embodiment the method comprises the use of one tag in the 5' primer and a different tag in the 3' primer and that this allows for a preferred two-step purification process wherein a ligand for either the N-terminal tag or C-terminal tag is used in the first step, and a ligand for the other peptide tag is used in the second purification step (see column 6, lines 5-36). Garvin et al further teach that this two step process will discriminate between polypeptides that result from transcription/translation of the entire amplified DNA template and those containing premature stop codons and/or those which result from internal translation initiation (ibid). Garvin et al also teach the use of mass spectrometry to determine the mass/identification of the translated protein (see, e.g., the Abstract).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Little et al with regard to the reaction mixture required to detect mutations in the APC gene with the teachings of Gavin et al with regard to the methods/reaction mixtures required to detect mutations in, e.g., the BRCA1 and BRCA2 genes because both Little et al and Gavin et al teach the use of PCR amplification and *in vitro* translation of epitope-tagged protein products in order to determine whether protein-altering mutations are present in a gene.

One of ordinary skill in the art would have been motivated to combine the teachings of Little et al with those of Garvin et al because Garvin et al teach that the use

of a second tag, different from the first, would allow for a two step purification process that could distinguish between full length protein products and those which were truncated and/or those which were the product of internal translation initiation. This is desirable because both Gavin et al and Little et al teach that the mass of the protein could be easily assessed via mass spectrometry in order to detect protein-altering mutations.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result when combining the teachings of Little et al with those of Garvin et al.

Claims 1, 9 and 11-13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Little et al (cited above) in view of Garvin et al (cited above) as applied to claims 1, 9 and 11-12 above, and further in view of Elion et al (*Current Protocols in Molecular Biology*, Unit 3.17, pages 3.17.1-3.17.10, 1993).

As explained above, Little et al in view of Garvin et al teach a PCR reaction mixture for amplifying a nucleic acid as a means of detecting and isolating a mutation in a genetic region, the reaction mixture comprising

a) a first oligonucleotide primer comprising i) a T7 promoter sequence, ii) a ribosome binding site sequence, iii) a start codon, iv) a sequence coding for a first epitope marker and v) a first region of complementarity to a region of the APC gene; and

b) a second oligonucleotide primer comprising i) at least one stop codon, and ii) a sequence encoding for a second epitope marker,

wherein said first epitope marker is SEQ ID NO: 5, a hexahistadine tag (see Little et al especially at column 3, lines 10-21 and 50-58; column 4, lines 20-22; column 9, lines 38-49; column 14, lines 1-3, 31-38, 51-55; column 15, lines 19-29) and the second epitope marker can be a FLAG tag such as Applicant's SEQ ID NO:7 (see Garvin et al at column 3, lines 59-67; column 4, lines 1-26; as well as Garvin et al's SEQ ID NO:2). Little et al in view of Garvin et al further teach such a reaction mixture wherein the reaction mixture includes APC template and wherein the 3' primer comprises a second region of complementarity to the template (see Little et al at column 4, line 22 and Garvin et al at column 4, lines 40-42).

Little et al in view of Garvin et al do not teach such a reaction mixture wherein the second region of complementarity is greater than 15 bases in length.

Elion teaches critical parameters for PCR reactions for constructing recombinant DNA molecules. Elion teaches that with regard to the design of primers, sequences with 16 to 20 nucleotides of homology to the target sequence should be chosen (see page 3.17.4, 1st column, 2nd full paragraph). Elion also teaches that "longer oligonucleotide of ~25 nucleotides should be used for AT–rich regions" and that in instances where genomic DNA is used as the source of target DNA, "the oligonucleotide primers should contain at least 20 nucleotides of homology to the target DNA to ensure that they anneal specifically" (ibid).

It would have been obvious for one of ordinary skill in the art to combine the teachings of Little et al in view of Garvin et al with those of Elion because Little et al in view of Garvin et al teach a PCR reaction mixture for the amplification of genes to detect protein-affecting mutations and Elion teaches well-established protocols with regard to parameters involved in PCR reactions, including primer design.

Given the teachings provided by Little et al and Garvin et al regarding the use of PCR reaction mixtures to detect protein-altering mutations, one of ordinary skill in the art interested in practicing the inventions of Little et al and Garvin et al would have been motivated to turn to the teachings of Elion et al for technical assistance in the design of primers for successful practice.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, the well-established PCR protocols established by the time of Applicant's filing, and absent evidence to the contrary, there would have been a reasonable expectation of success to result when combining the teachings of Little et al in view of Garvin et al with those of Elion.

Response to Arguments Concerning Claim Rejections – 35 USC § 103 (a)

Applicants' arguments filed December 20, 2007 have been fully considered but they are not persuasive.

The following grounds of traversal are presented:

Claim 1 comprises a pre-primer which lacks a region of complementarity to a region of a gene of interest, and none of the references teach that.

Both Little and Garvin teach the use of epitopes merely for purification in advance of mass spec., while the instant application teaches the use of both epitopes in an ELISA format for determining truncations without the use of gels or mass spec..

These arguments are not found persuasive for the following reasons.

Claim 1 does not specify what the gene of interest is. The "gene of interest" is also not defined by the specification. Therefore, any gene can be a gene of interest. Since this is the case, the pre-primer will inherently lack a region of complementarity to a region of a gene of interest, because a gene could be chosen which lacks a region of complementarity.

The intended use of the epitopes is irrelevant in product claims. The references combined teach all of the elements of the reaction mixture and the kit.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELE K. JOIKE whose telephone number is (571)272-5915. The examiner can normally be reached on M-F, 9:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

Michele K Joike, Ph.D.
Examiner
Art Unit 1636